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Pathologic Features and the Classification of Interstitial Pneumonia of Unknown Etiology

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Introduction

Interstitial pneumonia of unknown etiology or idiopathic interstitial pneumonia (IIP) has been recognized as a clinical entity for a group of patients with the following clinical features :

(1) The main feature is an exertional dyspnea with bilateral pulmonary infiltrates on chest x-rays. Pulmonary function tests show a restrictive dysfunction with reduced lung volumes. The arterial blood gas analysis shows hypoxemia which tends to get worse after exercise. The etiology is not known, even after careful investigation of the past medical history and the environmental history during life. The disease that possibly is complicated by a systemic disease, such as the collagen vascular disease, is excluded considering the present illness and the follow-up study.

(2) The clinical course may be classified into acute, subacute and chronic type. In the chronic type of the disease, an aggravated acute problem sometimes occurs with poor prognosis.

(3) For treatment, steroid hormones are not effective in most cases, although these drugs have been effective in a small number of cases.

Interstitial pneumonia of unknown etiology or IIP has been studied for almost a century, especially since the publishing of the reports by Hamman and Rich in 1935[1] and 1944[2]. Various terms (Table 1) have been proposed and used because of various clinical courses and pathologic findings. In early studies, most of the histopathologic findings that provided a basis for diagnosis were obtained by autopsy materials. However, an increase of open lung biopsy cases with interstitial pneumonia, particularly since the latter half of 1960's, has provided new informations that differed from those obtained by autopsy materials, hereby increasing knowledge of interstitial pneumonia[3-8]. Recently, new disease entities such as brochiolitis obliterans organizing pneumonia (BOOP)[9] and acute interstitial pneumonia (AIP)[10], based upon findings from open lung biopsy, have been reported. By using 468 open lung biopsy- and approximately 100 autopsy cases of diffuse infiltrative lung disease and the evaluation of the previous reports of interstitial pneumonia of unknown etiology, the author presents his views concering pulmonary disorders that are included in interstitial pneumonia of unknown etiology or IIP with their pathologic features and the classification[11].

Table 1. Nomenclature of interstitial pneumonia of unknown etiology

1897	Rindfleisch : Cirrhosis cystica pulmonum
1935	Hamman & Rich : fulminating diffuse interstitial fibrosis of the lungs
1944	Hamman & Rich : acute diffuse interstitial fibrosis of lungs
1948	Robbins : idiopathic pulmonary fibrosis
1950	Spain : acute interstitial fibrosis, chronic interstitial fibrosis
1951	Heppelston.: chronic diffuse interstitial fibrosis of the lungs
1957	Rubin : the "Hamman-Rich" syndrome
1957	Spain : chronic interstitial inflammation and fibrosis of the lungs
1960	Scadding : chronic diffuse interstitial fibrosis of the lung
1962	Herbert : interstitial pulmonary fibrosis
1964	Livingston : diffuse interstitial pulmonary fibrosis
1965	Stack : idiopathic diffuse interstitial lung disease
1965	Liebow : desquamative interstitial pneumonia (DIP)
1967	Liebow : interstitial pneumonias. UIP, BIP, DIP, LIP ,GIP.
1967	Scadding : diffuse fibrosing alveolitis
1968	Fox : idiopathic diffuse interstitial pulmonary fibrosis
1968	Haddad : idiopathic diffuse interstitial pulmonary fibrosis
1971	Turner-Warwick : cryptogenic fibrosing alveolitis
1972	DeRemee : classic interstitial pneumonitis fibrosis (CIP-F)
1976	Crystal : idiopathic pulmonary fibrosis (IPF)
1976	Katzenstein : diffuse alveolar damage (DAD)
1978	Winterbauer : diffuse interstitial pneumonitis
1978	Dreisen : idiopathic interstitial pneumonias
1978	Carrington : usual interstitial pneumonia (UIP)
1981	A Committee of the Ministry of Health and Welfare, Japan : idiopathic interstitial pneumonia (IIP)
1983	Tukiainen : cryptogenic fibrosing alveolitis
1983	Davison : cryptogenic organizing pneumonia (COP)
1985	Epler : bronchiolitis obliterans organizing pneumonia (BOOP)
1986	Katzenstein : acute interstitial pneumonia (AIP)
1987	Watters : idiopathic pulmonary fibrosis

I. Pathologic Features and the Classification of Interstitial Pneumonia of Unknown Etiology

Pathologic interstitial pneumonia is an intralobular inflammatory and fibrotic disorder of the lungs basically involving alveolar walls[11]. Various types of interstitial pneumonia of unknown etiology or IIP have been described. Such as diffuse alveolar damage (DAD) of unknown etiology or acute interstitial pneumonia (AIP)[3,5,10,12], usual interstitial pneumonia (UIP)[13], bronchiolitis obliterans organizing pneumonia (BOOP)[9], desquamative interstitial pneumonia (DIP)[13,14], and lymphocytic interstitial pneumonia (LIP)[15]. A small number of cases are labelled to be unclassified interstitial pneumonia (Unclass IP) (Table 2).

1. Diffuse alveolar damage

Diffuse alveolar damage is a diffuse pulmonary lesion characterized by formatin of hyaline membranes in the early stage (Table 3)[3,5,7,12]. Many causes are listed for the etiology of DAD, taking into account that DAD can be reversed if the causes are eradicated during the clinical course[3]. DAD is the histopathologic expression of the adult respiratory distress syndrome

Table 2. Classification of interstitial pneumonia of unknown etiology

1. Diffuse alveolar damage (DAD)
2. Usual interstitial pneumonia (UIP)
3. Bronchiolitis obliterans organizing pneumonia (BOOP)
4. Desquamative interstitial pneumonia (DIP)
5. Lymphocytic interstitial pneumonia (LIP)
6. Unclassified interstitial pneumonia (Unclass IP)

(ARDS), especially in the fatal cases, although also other diseases such as acute eosinophilic pneumonia or BOOP may be presented as acute diffuse infiltrative lung diseases.

From the histopathlogic point of view, DAD shows a relatively broad spectrum of lesions which are divided into acute, early or exudative stage, and, organizing, reparative or late stage (Table 3)[3,5,7]. In cases following respirator therapy for months, lungs may show multiple small cystic lesions measuring 1-3 mm. Histologically, the small cystic lesions are usually dilated alveolar ducts, lined with hyaline membranes or organized hyaline membranes. They are surrounded with collapsed adjacent alveoli (Fig. 1).

DAD of unknown etiology was labelled as acute interstitial pneumonia (AIP) by Katzenstein et al.[10].

A case of idiopathic DAD : A 61 year-old woman born in 1926 underwent a left thoracotomy for lung biopsy on May 26, 1987. She developed swellings of hand joints in January 1987 followed by general malaise and fever in March 1987 when she was hospitalized. Physical examinations revealed crackles on the chest, while a chest x-ray showed bilateral pulmonary infiltrates. Thirty mg of Predonin per day was given. However, she developed dyspnea in May 1987. In spite of a steroid pulse therapy with respirator after the lung biopsy, she died

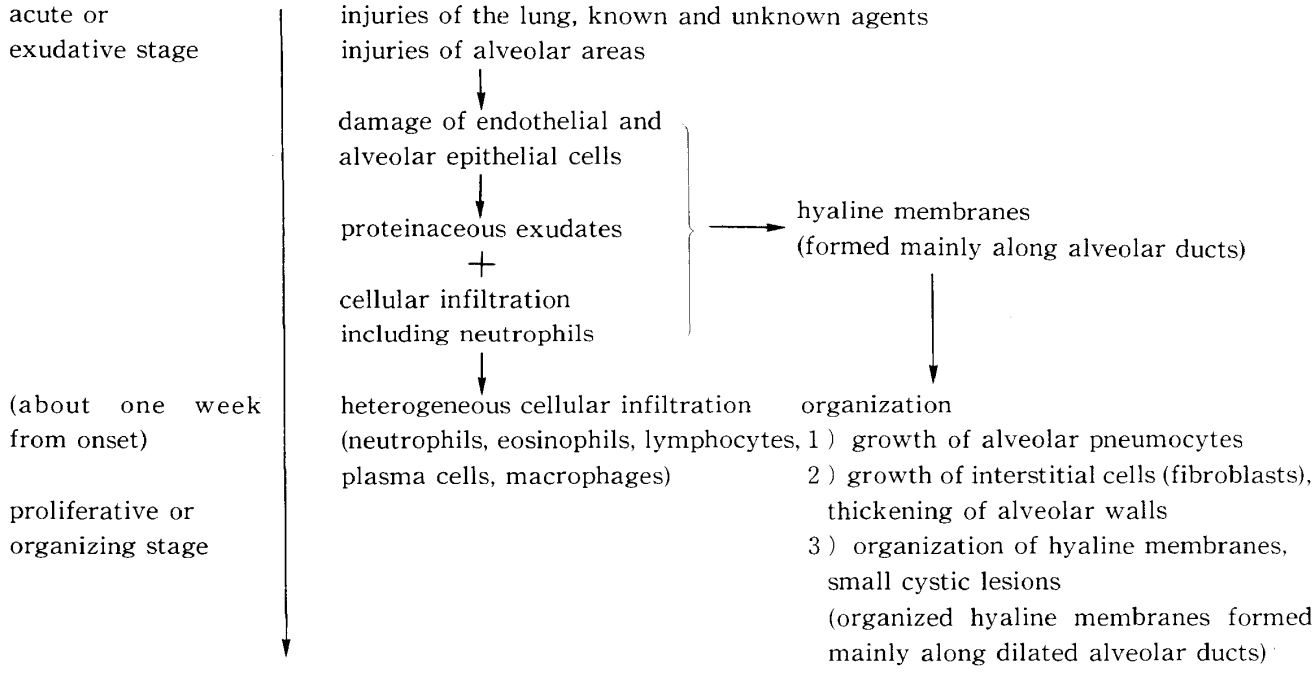

Fig. 1. Course of diffuse alveolar damage

Table 3. Features of diffuse alveolar damage

Early stage :
1. Extensive damage to alveolar lining cells associated with hyaline membranes
2. Intra-alveolar edema, exudate, or hemorrhage
3. Edematous and widened interstitium with variable numbers of mononuclear cells
Reparative stage :
1. Numerous regenerative type II lining cells
2. Organization within airways

Yousem, Colby & Carrington (1985)

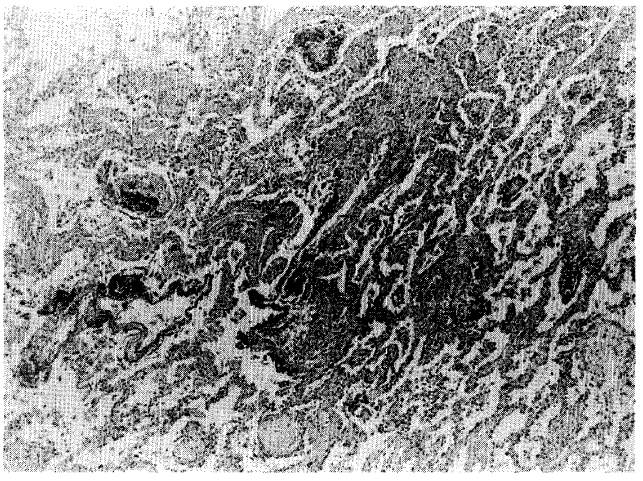

Fig. 2. DAD. The open lung biopsy sample shows a diffuse fibrous thickening of alveolar walls, hyaline membranes, hyalinous exudates with or without organization and several granulation tissues covered with epithelial cells (H & E, 4x10).

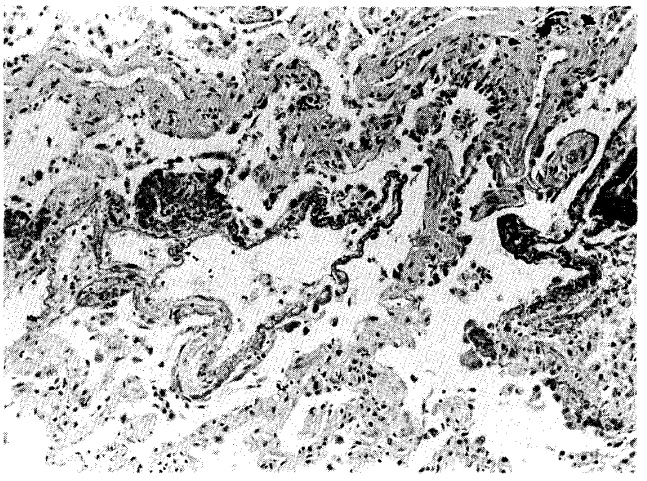

Fig. 3. DAD. Higher magnification of Fig. 2 showing hyaline membranes and hyalinous exudates in terminal air spaces. Alveolar walls show a fibrous thickening and are covered with hyperplastic cuboidal cells, which some of them show mild nuclear atypia. A few neutrophils infiltrate in the air spaces (H & E, 10x10).

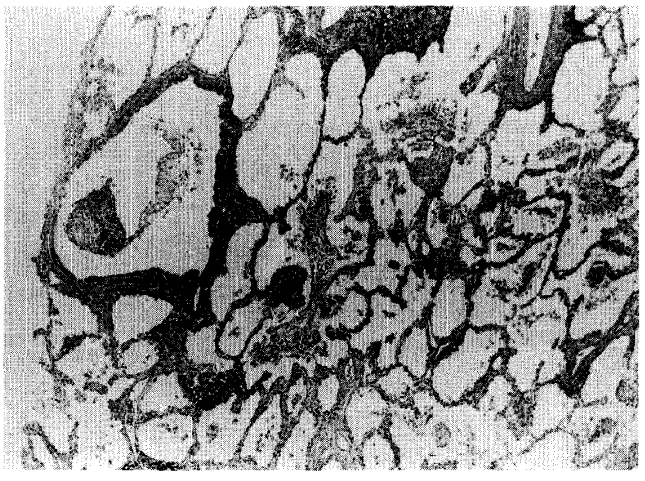

Fig. 4. DAD. Another view of the same biopsy sample with Fig. 2 reveals a diffuse fibrous thickening of alveolar walls, granulation tissues formed in alveolar ducts and an organized hyalinous exudate in a membranous bronchiole (left). Although mild in lesion, the last finding is an example of brochiolitis obliterans in the pathologic spectrum of DAD (H & E, 4x10).

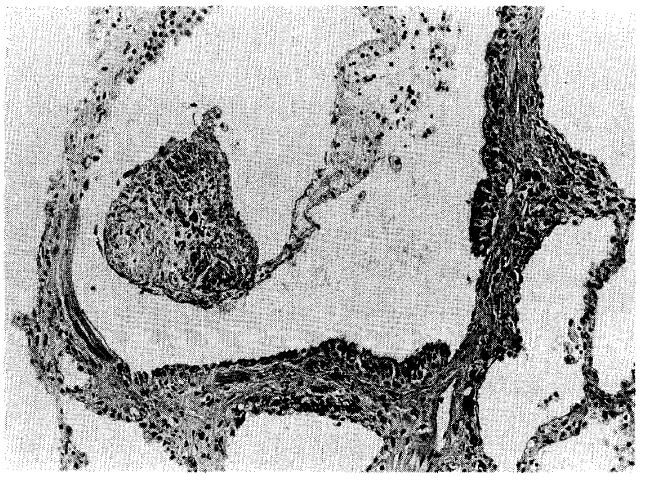

Fig. 5. DAD. Higher magnification of Fig. 4 showing an organized hyalinous exudate in the membranous brochiole (a finding of luminal type of bronchiolitis obliterans). The peribronchiolar tissue shows anthracosis (H & E, 10x10).

of progressive respiratory insufficiency on June 30, 1987.

The biopsy sample from the left upper lobe showed a diffuse fibrous thickening of alveolar walls, multiple hyalinous exudates, Masson bodies in alveolar spaces and hyaline membranes along alveolar ducts. The alveolar walls showed a mild infiltration of lymphocytes and plasma cells (Fig. 2 and 3). A few bronchioles showed granulation tissues or organized hyalinous exudates in the lumen. These findings refer to bronchiolitis obliterans in DAD (Fig. 4 and 5). Microorganisms including viruses were negative after culture of the biopsy sample.

Autopsy samples of the lungs showed many marked features of organized diffuse alveolar damage with granulation tissues formed in bronchioles.

2. Usual interstitial pneumonia

The diagnostic criteria for UIP have been described in the study by Carrington et al. (Table 4)[13] in which 92.5% of the 93 study subjects were open lung biopsy cases. To recognize UIP, the finding of highly variegated structure, including the entire spectrum from normal alveolar walls to fibrotic, end-stage lesions in the same tissue sample is most important[11]. Fibrotic lesions in UIP are heterogeneous in spacial distribution and in progression. The distribution of fibrotic lesions in UIP is patchy in the intra-lobular lung parenchyma both in spacial distribution being interspersed with normal alveolar walls and in progressing to fibrotic processes where smooth muscle proliferation is noted in the fibrotic lesions[11].

A case of idiopathic UIP : A 65 year-old man born in 1921 underwent a left thoracotomy for lung biopsy in October 1987. He was examined as having bilateral lower pulmonary infiltrates on a chest x-ray in May 1984. In October 1986 he developed exertional dyspnea and cough. Crackles on the chest were noted at the first consultation in July 1987 with chronic bilateral pulmonary infltrates on a chest x-ray. After the biopsy, 60 mg of Predonin per day was given. He was readmitted in March 1988 when the arterial oxygen pressure was 33. 7mmHg while breathing room air. In spite of a steroid pulse therapy for several times, he died of progressive respiratory failure in October 1988.

The lung biopsy samples showed patchy and heterogeneous interstitial fibrotic lesions, interspersed with normal alveolar walls with subpleural honeycombing and focal infiltration of lymphocytes in alveolar walls (Fig. 6-9). Hyaline membranes were not observed.

Table 4. Criteria for usual interstitial pneumonia

1. Highly variegated structure often including the entire spectrum from normal alveolar walls to fibrotic, end-stage lesions in the same tissue sample
2. Dense, pleomorphic interstitial cellular infiltrate including many lymphocytes and monocytes but relatively few eosinophils
3. Variegated epithelial lining in small air spaces ranging from large, rounded cells on less damaged alveolar walls to cuboidal, columnar, ciliated, goblet and squamous cells on more scarred alveolar walls
4. Few cells, mostly macrophages, in small air spaces
5. Some proteinaceous exudates, especially in alveoli with early lesions

Nonspecific features:
- fibrosis
- honeycombing

Carrington, C. B. et al. (1978)

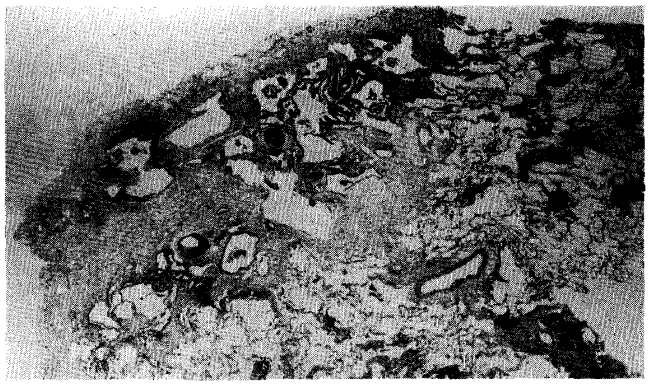

Fig. 6. UIP. The open lung biopsy sample shows honeycombing (upper middle) and dense fibrotic lesions predominantly in the subpleural zones of lobules. Lobules show a patchy distribution of fibrotic processes interspersed with normal alveolar walls. Muscular pulmonary arteries show a sclerosis of the eccentric type (H & E, 1x10).

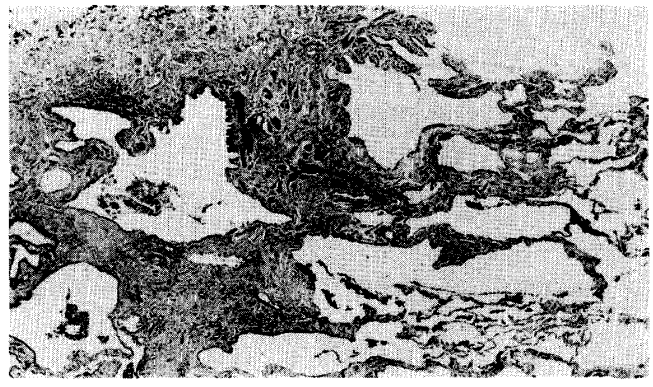

Fig. 7. UIP. Higher magnification of Fig. 6 showing smooth muscle proliferation in the subpleural dense fibrotic lesion, a fibrous thickening of alveolar walls, and, parts of normal alveolar walls (lower right)(H & E, 4x10).

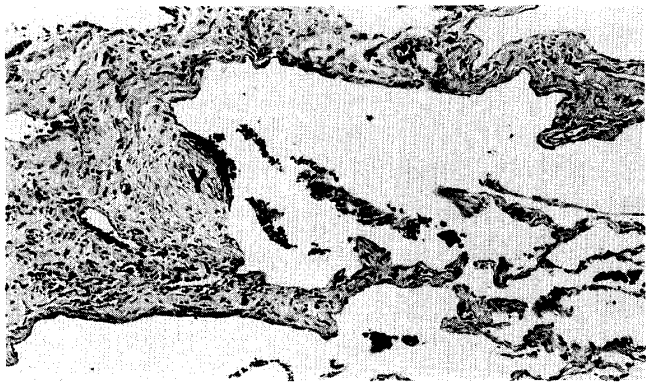

Fig. 8. UIP. Higher magnification of Fig. 7 showing a young connective tissue formation (Y) or a fibroblastic lesion protruding into the terminal air space that is covered with epithelial cells, and, a fibrous thickening of alveolar walls (H & E, 10x10).

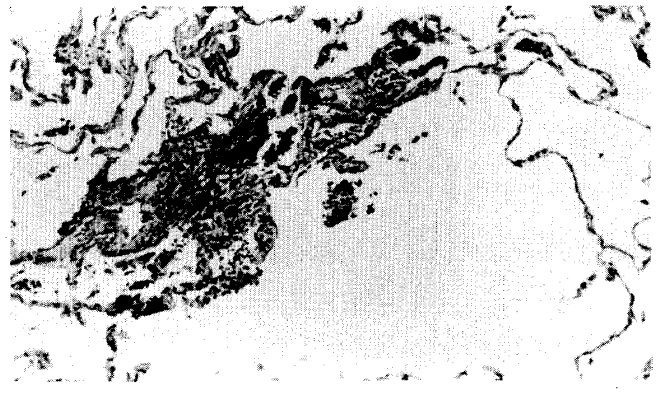

Fig. 9. UIP. Higher magnification of Fig. 6 showing focal infiltration of lymphocytes in alveolar walls and in adjacent air spaces. The neighboring alveolar walls are normal (H & E, 10x10).

3. Bronchiolitis obliterans organizing pneumonia

Bronchiolitis obliterans organizing pneumonia is a type of inflammatory and fibrotic pulmonary lesion showing (1) bronchiolitis obliterans with plugs of granulation tissue involving bronchioles and alveolar ducts, (2) organizing pneumonia with extension of the organization from distal alveolar ducts into alveoli, with variable degrees of interstitial infiltration of mononuclear cells and (3) patchy distribution, with preservation of background architecture of the pulmonary parenchyma (Table 5)[9]. For the diagnosis of BOOP, in addition to negative results of organisms in microbiological cultures and histologic stains using Ziehl-Neelsen's and Grocott's methenamine silver methods, it is necessary to notice that the findings listed in Table 6 were absent in the biopsy samples, which were taken from the most involved site of the lung[11].

A case of idiopathic BOOP : A 57 year-old man born in 1927 underwent a left thoracotomy for lung biopsy on August 8, 1984. He developed cough and exertional dyspnea in June 1984. Chest x-rays showed bilateral pulmonary infiltrates in the lower lung fields. Crackles were noted on the auscultation of lungs. After the lung biopsy, he was followed up without a steroid hormone treatment for more than three years, in meanwhile symptoms and pulmonary infiltrates showed spontaneous regression[16].

Lung biopsy samples showed intra-lobular inflammatory lesions with granulation tissues in respiratory bronchioles, alveolar ducts and alveoli. Besides, a mild fibrous thickening of alveolar walls with interstitial

Table 5. Pathologic features of bronchiolitis obliterans organizing pneumonia

1. Bronchiolitis obliterans
   plugs of granulation tissue involving bronchioles and alveolar ducts
2. Organizing pneumonia
   extension of the organization from distal alveolar ducts into alveoli, with variable degrees of interstitial infiltration of mononuclear cells
3. Patchy distribution, with preservation of background architecture of the pulmonary parenchyma

Table 6. Differential diagnosis of bronchiolitis obliterans organizing pneumonia

Findings negative for BOOP	Suspected Pulmonary Disorders
1. Necrosis or infarction	Infection, Abscess, Pulmonary infarction, Lymphoproliferative disorder, Wegener's granulomatosis (WG)
2. Marked cellular infiltration in pleura or interlobular septa	Lymphoproliferative disorder, Eosinophilic pneumonia
3. Solid nodular proliferation of lymphocytic cells	Lymphoproliferative disorder
4. Marked hyalinous exudates	Diffuse alveolar damage including infectious etiology, Eosinophilic pneumonia, Lymphoproliferative disorder,
5. Hyaline membranes	Diffuse alveolar damage
6. Granulomatous lesions	Infection, Hypersensitivity pneumonitis, Lymphoproliferative disorder, Eosinophilic pneumonia, WG
7. Marked infiltration of eosinophils more than observed in UIP	Eosinophilic pneumonia, Wegener's granulomatosis
8. Marked reparative metaplastic changes of bronchiolar epithelial cells	Infection (mycoplasma, viruses)
9. Marked infiltration of PMN neutrophils	Infection, Pulmonary abscess, Acute bronchiolopneumonia
10. Angiitis	Infection, Wegener's granulomatosis, Lymphoproliferative disorder

infiltration of lymphocytes and plasma cells were demonstrated (Fig. 10-12).

4. Desquamative interstitial pneumonia

Desquamative interstitial pneumonia was originally described by Liebow et al. on occasion of 18 open lung biopsy cases, including one case with a postmortem examination[14]. The histopathologic criteria for DIP have been described by Carrington et al. (Table 7)[13] and DIP has been pointed out as showing a relatively favorable prognosis, when compared with UIP[13]. Mainly by electron microscopic studies, large mononuclear cells in the terminal air spaces in DIP were pointed out to be macrophages instead of desquamated pneumocytes. Recently, a minor part of cases, previously assessed as DIP, were recognized to be respiratory bronchiolitis -associated interstitial lung disease[17].

A case of idiopathic DIP : A 55 year-old male born in 1923 underwent an open lung biopsy in June 1978. He suffered from cough and white sputum for about three years and exertional dyspnea for one year. Velcro rales

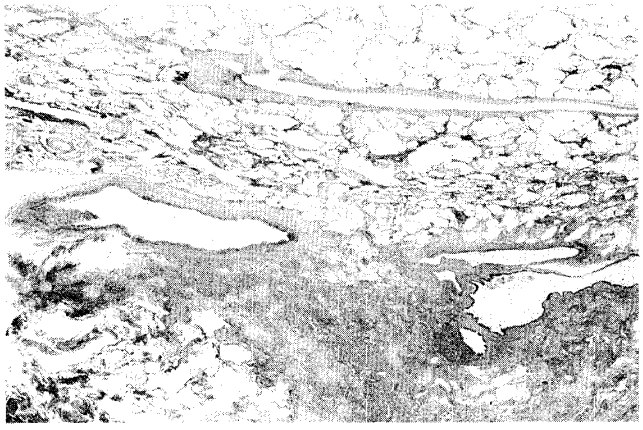

Fig. 10. BOOP. The open lung biopsy sample shows granulation tissues formed in alveolar ducts, alveolar spaces and bronchioles. The lesion of organizing pneumonia is marked in the lower middle portion of the view. Connective tissues around bronchiolovascular trees are not involved essentially (H & E, 1x10).

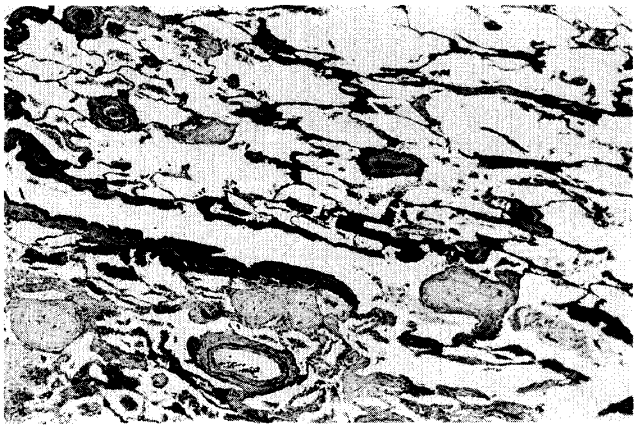

Fig.11. BOOP. Higher magnification of Fig. 10 showing granulation tissues formed in a respiratory bronchiole and alveolar ducts. These granulation tissues have some connections with the wall of the bronchiole or alveolar ducts. Alveolar walls show a mild fibrous thickening and an infiltration of lymphocytes and plasma cells (H & E, 4x10).

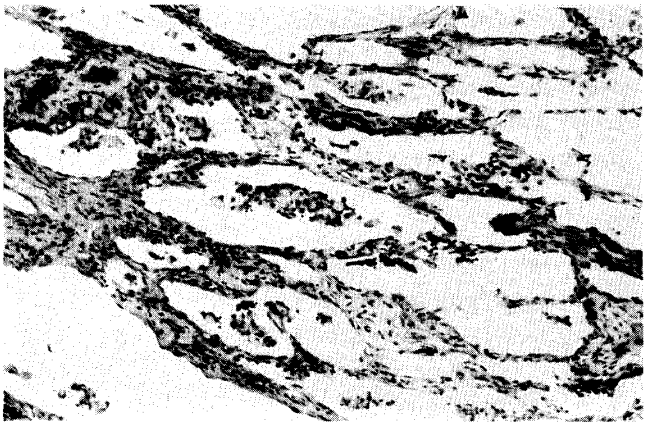

Fig. 12. BOOP. Higher magnification of Fig. 10 showing interstitial lesions with a fibrous thickening of alveolar walls and an infiltration of lymphocytes and plasma cells. Terminal air spaces contain foamy cells and lymphocytes (H & E, 20x10).

were noted on the chest auscultation. Chronic bilateral pulmonary infiltrates were noted on chest x-rays especially in the lower lung fields. After the biopsy, 40mg of Predonin per day was given without improvements. He died of respiratory failure in July 1982.

Table 7. Criteria for desquamative interstitial pneumonia

1. Relative uniformity of the lesion throughout the tissue sample
2. Sparse interstitial cellular infiltrate, including an appreciable proportion of plasma cells and eosinophils
3. Prominent lining of alveoli by large, rounded cells
4. Abundant mononuclear cells filling many small air spaces
5. Little if any proteinaceous exudate in air spaces or interstitium

non-specific features:
- fibrosis
- honeycombing

Carrington, C. B. et al. (1978)

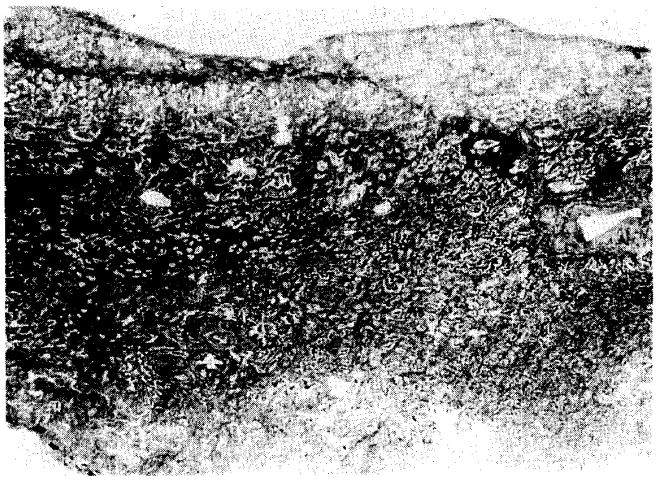

Fig. 13. DIP. The open lung biopsy sample shows diffuse intralobular inflammatory and fibrotic lesions throughout the sample with some lymphoid follicles (H & E, 1X10).

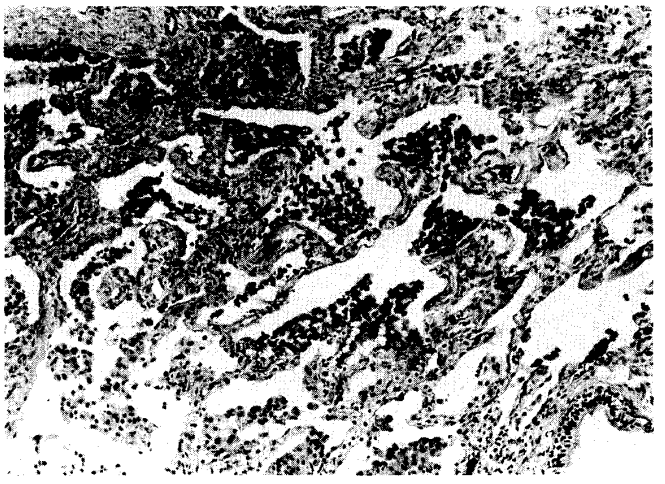

Fig. 14. DIP. Higher magnification of Fig. 13 showing a diffuse fibrous thickening of alveolar walls with an infiltration of lymphocytes, plasma cells and several eosinophils. Air spaces of alveoli and a bronchiole have many large mononuclear cells (H & E, 10x10).

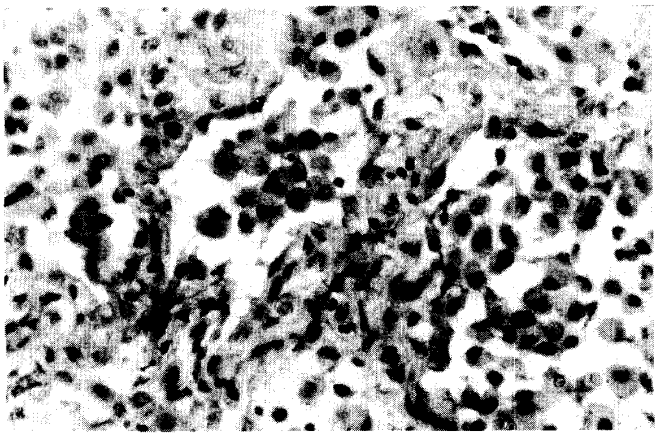

Fig. 15. DIP. Higher magnification of Fig. 13 showing a fibrous thickening of alveolar walls covered with hyperplastic cuboidal alveolar lining cells and many large mononuclear cells in air spaces (H & E, 20x10).

Lung biopsy samples showed relatively homogeneous intra-lobular chronic inflammatory lesions with a diffuse fibrous thickening of alveolar walls and an accumulation of large mononuclear cells in alveolar spaces. Several eosinophils infiltrated in the air spaces and interstitium with lymphoid cells (Fig 13-15).

5. Lymphocytic interstitial pneumonia

Lymphocytic interstitial pneumonia is a chronic interstitial pneumonia and shows a marked infiltration of lymphocytes and plasma cells, compared with cases of UIP. Honeycomb-

Table 8. Criteria for lymphocytic interstitial pneumonia

1. A chronic interstitial pneumonia
2. Diffusely involved by a dense lymphoid infiltrate in the pulmonary parenchyma
3. Polymorphous infiltrates including lymphocytes, plasma cells, histiocytes and epithelioid histiocytes
4. Interstitial fibrosis and honeycombing

Colby, T. V. and Carrington, C. B. (1983)

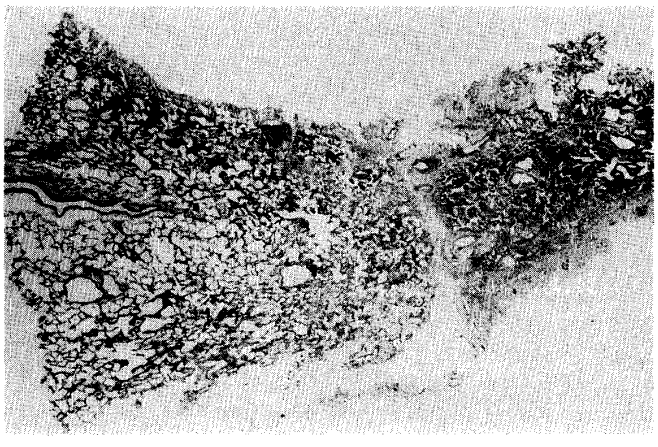

Fig.16. LIP. The open lung biopsy sample shows a diffuse thickening of alveolar walls with a cellular infiltration and several lymphoid follicles. The visceral pleura is not involved essentially (H & E, 1x10).

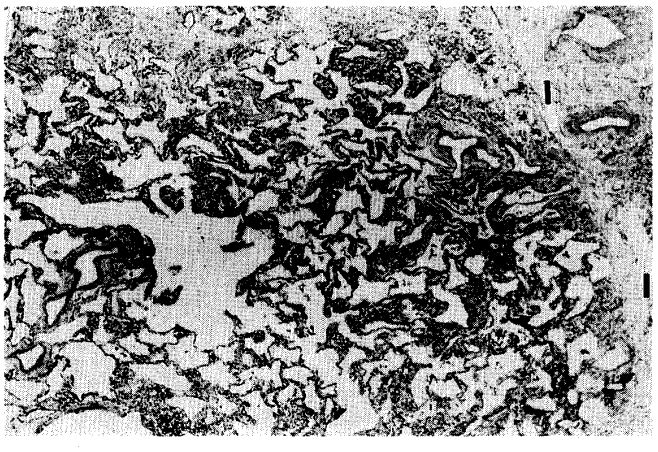

Fig. 17. LIP. Higher magnification of Fig. 16 showing a diffuse infiltration of lymphocytes, plasma cells and a few eosinophils in the alveolar walls. Interlobular septa (I) are not involved essentially (H & E, 4x10).

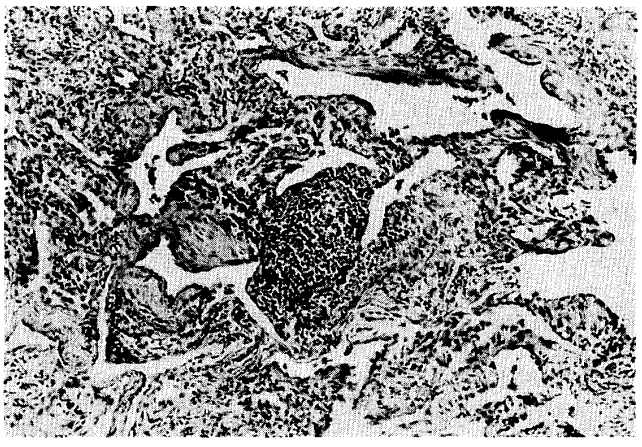

Fig. 18. LIP. Higher magnification of Fig. 16 showing an infiltration of lymphocytes in the alveolar walls. Several young connective tissues or fibroblastic lesions are formed protruding to the terminal air spaces (H & E, 20x10).

ing and occasional small granulomas may be formed (Table 8)[15].

A case of idiopathic LIP : A 33 year-old female born in 1954 underwent a thoracotomy in July 1988 for the treatment of bilateral spontaneous pneumothoraces. She had never smoked. She developed cough in May 1987 and shortness of breath in September 1987. Bilateral pulmonary infiltrates were noted on a chest x-ray in April 1988 at the time of consultation. She developed spontaneous bilateral pneumothoraces in June 1988. After the thoracotomy, she was discharged in August 1988 and has been followed up since.

Lung biopsy samples from the bilateral lungs showed a diffuse infiltration of lymphocytes, plasma cells and histiocytic cells in alveolar walls with fibrotic changes and formation of lymphoid follicles. Although blebs were formed in several places of the visceral pleura, interlobular septae were not involved essentially (Fig.16-18).

6. Current evaluation of Liebow's classification of interstitial pneumonia

A classification of interstitial pneumonia proposed by Liebow[18-20] is described in Table 9. The term of diffuse alveolar damage was coined by Liebow[18] for the diffuse inflammatory pulmonary disorders, characterized with a formation of florid numbers of hyaline membranes. The term of UIP was also coined by Liebow[18]. UIP is an abbreviation of diffuse alveolar damage and the "usual" interstitial pneumonias[18], the classical, "usual" or undifferentiated interstitial pneumonia[19], and, classical or 'usual' interstitial pneumonia[20]. Four cases reported by Hamman and Rich in 1944[2] were considered to be classic cases of Liebow's description of UIP[18-20]. Hyaline membranes were supposed to have been observed not only in autopsy cases

Table 9. Current evaluation of Liebow's classification of interstital pneumonia

Liebow (1967, 1968, 1975)	Currently
DAD and UIP (Liebow's UIP)	DAD
	UIP (Carrington)
BIP	BOOP (1985)
DIP (1965)	DIP
LIP[1)]	LIP[2)]
	Lymphoproliferative disorder
GIP	Hard-metal lung disease

DAD : diffuse alveolar damage
UIP : usual interstitial pneumonia
BIP : bronchiolitis obliterans and diffuse alveolar damage
DIP : desquamative interstitial pneumonia
LIP[1)] : lymphoid interstitial pneumonia
LIP[2)] : lymphocytic interstitial pneumonia
GIP : giant cell interstitial pneumonia
BOOP : bronchiolitis obliterans organizing pneumonia

of interstitial pneumonia with acute clinical course, but also in autopsy cases of interstitial pneumonia with chronic clinical course. Therefore, he thought that honeycombing (chronic honeycombing that is formed in the chronic clinical course) was formed in the process of diffuse alveolar damage and a hyaline membrane formation was considered to be an essential finding of pathology and pathogenesis of UIP[18-20]. Pulmonary lesions of diffuse alveolar damage were described as acute UIP or organizing UIP by Liebow in 1975[20].

Honeycombing is basically a macroscopic descriptive term and may be found in various pulmonary disorders. However, small cystic lesions in the process of diffuse alveolar damage are lined with hyaline membranes or organized hyaline membranes, usually along dilated alveolar ducts. While small cystic lesions in the process of UIP[13] are usually formed at the level of respiratory bronchioles and lined with epithelial cells, often being filled with mucin. The author supposes that pulmonary lesions of UIP observed according to Liebow's criteria include three major situations ; ① DAD, ② DAD superimposed on UIP (Carrington, 1978)[13], and ③ UIP (Carrington, 1978)[13] (Table 9).

BIP is the abbreviation of bronchiolitis obliterans and diffuse alveolar damage[18,19], or bronchiolitis obliterans with classical interstitial pneumonia[20]. Diffuse alveolar damage may show granulation tissues or organized exudates, formed in bronchioles especially in the organizing stage. One among 30 cases of BOOP had postmortem examinations 59 months after the open lung biopsy, and, showed diffuse alveolar damage in the autopsied lungs. The pulmonary lesions of BOOP that were observed at the time of lung biopsy were difficult to identify. Therefore, the concept of Liebow's term BIP may also include BOOP in some cases, although Liebow's term is considered basically to be a pathologic spectrum of diffuse alveolar damage observed at the autopsy studies (Table 9).

DIP has been described on occasion of open lung biopsy cases[13,14]. The concept of DIP is not changed basically although a small number of the cases has been determined as respiratory bronchiolitis-associated interstitial lung disease[17].

Lymphoid interstitial pneumonia cases have been divided into cases of lymphocytic interstitial pneumonia (a type of chronic interstitial pneumonia), and, cases of lymphoproliferative lung disease[15].

Cases of giant cell interstital pneumonia are considered basically to be a fibrotic lung disease due to the inhalation of hard metals[5,21].

Table 10. Clinical settings of idiopathic pulmonary fibrosis

1. Respiratory symptoms: exertional dyspnea, cough
2. Bilateral crackles, clubbing of fingers
3. Chest x-rays: bilateral chronic infiltrates
4. Slowly progressive symptoms and CXR findings in blocks of a year or several months
5. Sparse non-respiratory symptoms
6. Absence of direct causes including inhalation agents

II. Idiopathic Pulmonary Fibrosis (Usual Interstitial Pneumonia)

1. A concept of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a clinical term, while usual interstitial pneumonia (UIP) is a pathologic term. IPF has been used in the broader sense by some investigators[22] and cryptogenic fibrosing alveolitis is said to be synonymous with IPF[23,24]. For all that, IPF was described at the National Institute of Health Conference in November 1975 as "a fatal disease that starts as an alveolitis and progresses to interstitial fibrosis"[25]. At that time, the Hamman-Rich syndrome[1,2] and cases of collagen vascular diseases with similar pulmonary disorders were included in cases of IPF. The pathology of IPF was described to be UIP or DIP. Later in 1979, cases of interstitial pneumonia associated with collagen vascular diseases were separated. In 1988, the pathology of IPF was described to be UIP, DIP, or a mixture of UIP and DIP[26]. Most investigators are said to believe that DIP represents an early stage of IPF, UIP represents a more advanced stage of IPF [22], and UIP and DIP are viewed as parts of IPF[27]. However, the most important point in the description of IPF by Crystal et al. is that IPF is a fatal disorder of lungs[25].

According to the author's observations, ① the frequency of idiopathic DIP is 1/10 or less compared with that of idiopathic UIP ; ② pathologic features of UIP were observed even in early asymptomatic cases of idiopathic UIP with bilateral pulmonary infiltrates ; ③ although cases of DIP are poor in the prognosis, one among five cases of DIP showed improvement with

Table 11. Acute exacerbation of idiopathic pulmonary fibrosis

1. Acute exacerbation of dyspnea in blocks of several days
2. Associated worsening of bilateral pulmonary infiltrates on chest x-rays
3. Often associated with acute inflammatory changes including fever
4. Apparent absence of infectious etiology

Table 12. A review study of suspected IPF cases

(1) 59 of 65 suspected IPF cases (91%) were confirmed as having IPF (UIP).	
open lung biopsy	47 cases
autopsy	23 cases
(open lung biopsy & autopsy	11 cases)
(2) 31 of the 59 IPF (UIP) cases died.	
(3) Direct causes of death of the 31 cases were assessed clinically :	
pulmonary lesions of IPF	23 cases
(acute exacerbation of IPF	12 cases)
pulmonary infection	2 cases
pulmonary carcinoma	5 cases
carcinoma of gallbladder	1 case

a steroid hormone treatment (unpublished observation by the author et al.). Therefore, some cases of DIP may show better prognosis, which is against the Crystal's concept of IPF being fatal. Consequently, the author thinks that it is better to separate the cases of UIP from those

Table 13. IPF autopsy cases with acute exacerbation clinically

Case	Age (years)	Sex	Duration (months) between first consultation and death	Duration (months) between acute worsening and death	Major pulmonary lesions in addition to UIP at the time of autopsy
(1)	46	M	67M	0.5M	org DAD, hemorrhage, abscess (aspergillus)
(2)	64	M	1M	0.5M	DAD
(3)	58	M	65M	1.5M	org DAD
(4)	37	M	3M	3M	org DAD, pneumonia
(5)	76	M	1M	2M	DAD
(6)*	69	M	47M	0.2M	DAD, hemorrhage
(7)*	65	M	37M	0.7M	org DAD
(8)*	73	M	19M	1.2M	org DAD
(9)	67	F	2M	4.1M	org DAD
(10)	65	F	11M	0.6M	org DAD
(11)	70	F	23M	0.7M	org DAD, hemorrhage
(12)*	63	F	17M	0.2M	Necrotizing pneumonia
mean	62.8		24.4M	1.3M	

* : open lung biopsy case
DAD : diffuse alveolar damage org DAD : organizing DAD

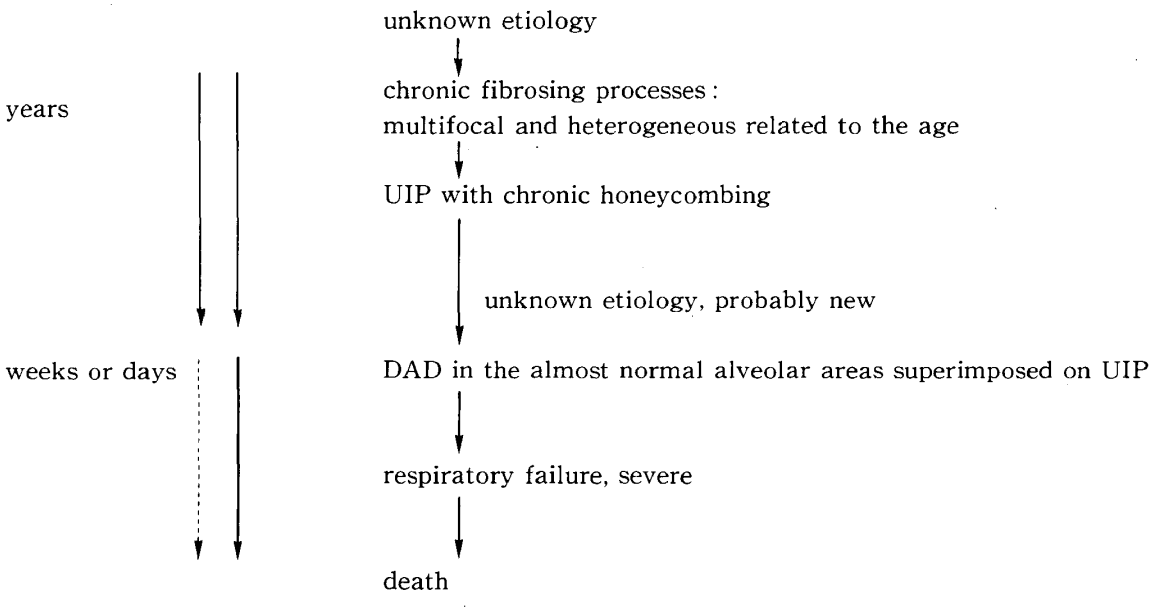

Fig. 19. Course of IPF (UIP)

of DIP. Furthermore, that IPF is used synonymously with idiopathic UIP, especially when pulmonary pathology is confirmed to be UIP by an open lung biopsy.

2. Clinical features of idiopathic pulmonary fibrosis and acute worsening

IPF is a suspicious diagnosis in the clinical settings as follows : the patient has respiratory symptoms such as exertional dyspnea and cough, and, physical findings of bilateral late inspiratory fine crackles on the lungs in combination with or without clubbing of fingers. Chest x-rays show bilateral chronic infiltrates, predominantly in outer and lower zones of lung fields. Pulmonary function tests show a restrictive dysfunction and a reduced diffusing capacity of the lungs. An arterial blood gas analysis shows hyoxemia, which becomes worse after exercise. These symptoms and findings show a slow progress in blocks of one year or several months with sparse non-respiratory symptoms and absence of direct causes, including inhalation agents (Table 10).

Patients with IPF sometimes show acute worsening or exacerbation of symptoms and findings with an apparent absence of causes such as infectious etiology, even after a clinical work-up (Table 11).

3. A clinicopathologic review of suspected IPF cases

The author reviewed 65 suspected IPF cases at the Chest Disease Research Institute, Kyoto University, together with Richard A. DeRemee, M. D. and Thomas V. Colby, M. D. from the Mayo Clinic, Rochester, Minnesota, U. S. A. . Among the 65 cases, which underwent an open lung biopsy and/or a postmortem examination, 59 cases were confirmed as having idiopathic pulmonary fibrosis (usual interstitial pneumonia). Until the time of the review in November

Table 14. 106 open lung biopsy cases at the Chest Disease Research Institue, Kyoto University (January 1983-August 1989)

Pulmonary disorders	No. of cases
Infection	5 (TB 3 ; fungal 2)
Pneumoconiosis	4 (asbest 2 ; others 2)
Neoplasm	7 (LAM 2 ; IVBAT 1 ; others 4)
Interstitial pneumonia of unknown etiology	52 (49%)
IPF (UIP)	42
BOOP	7
LIP	1
Unclass IP	2
Collagen vascular diseases	15 (UIP 6 ; Unclass IP 3 ; others 6)
Eosinophilic granuloma	4
Sarcoidosis	5
Hypersensitivity pneumonitis	4
Diffuse panbronchiolitis	3
Others	7

1988, 31 cases died. According to the clinical assessment, 23 cases died of worsened pulmonary inflammatory disorders. Twelve of them were assessed to have died of acute worsened IPF (Table 12).

A pathologic study of the 12 IPF autopsy cases, with a clinical assessement of acute exacerbation, revealed that the direct cause of death in 10 cases (83%) was due to diffuse alveolar damage, superimposed on the chronic pulmonary process of usual interstitial pneumonia with chronic honeycombing (Table 13). In these 10 cases, the causes of superimposed diffuse alveolar damage were not known, even after bacteriological examinatioins of autopsied lung tissues. Therefore, these ones were supposed to have undergone the clinical course as shown in Fig. 19.

4. A high frequency of IPF (UIP) among interstitial pneumonia of unknown etiology

Among 106 open lung biopsy cases, performed for the diagnosis of diffuse infiltrative lung diseases at the Chest Disease Research Institute, Kyoto University, between January 1983 and August 1989, 52 cases (49%) were interstitial pneumonia of unknown etiology or IIP. Among the 52 cases, IPF (UIP) occurred most frequent (42 cases or 81%) with idiopathic BOOP as the second occurring (7 cases or 13%)(Table 14). Other types of interstitial pneumonia of unknown etiology or IIP were less than 6%. These open lung biopsy samples were usually taken from two sites of two different lobes of a lung. The biopsy samples were examined by bacteriological and histopathologic methods.

Summary

Currently, five types of interstitial pneumonia of unknown etiology or IIP have been described; DAD, UIP, BOOP, DIP and LIP. A summary of the features of clinical course, prognosis and therapeutic effects to steroid hormone treatment of the five types of interstitial pneumonia of unknown etiology or IIP is given in Table 15[28]. Among the previous mentioned

Table 15. Clinicopathlogic classification of intersititial pneumonia of unknown etiology

Pathology	Clinical Diagnosis	Clinical Course	Steroid Response	Prognosis
DAD	AIP	acute	poor	poor
BOOP	BOOP	subacute	good	good
UIP	IPF	chronic	poor	poor
DIP	DIP	chronic	not good	not good
LIP	LIP	chronic	various	various

AIP : acute interstitial pneumonia
IPF : idiopathic pulmonary fibrosis

52 open lung biopsy cases of interstitial pneumonia of unknown etiology or IIP, for which an open lung biopsy was necessary for diagnosis[26], the majority of those cases (81%) was IPF (UIP) while idiopathic BOOP occurred as the second in frequency (13%). These data will help in understanding the clinical outcome and the therapeutic response to steroid hormone treatment in cases of interstitial pneumonia of unknown etiology or IIP, because idopathic UIP is slowly progressive and usually not responsive to steroid[13] while idiopathic BOOP is usually responsive to steroid hormone treatment and may regress even spontaneously[9,11,16]. Cases of IPF (UIP) should have revolutional modalities for therapy.

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References

1) Hamman, L. and Rich, A. R.: Fulminating diffuse interstitial fibrosis of the lungs. Trans Am. Clin. & Climatol. Asson., 51: 154-163, 1935.

2) Hamman, L. and Rich, A. R.: Acute diffuse interstitial fibrosis of the lungs. Bull. Johns Hopkins Hosp., 74: 177-212, 1944.

3) Katzenstein, A-L. A. and Askin, F. B.: Surgical Pathology of Non-Neoplastic Lung Disease. W. B. Saunders Co., Philadelphia, 1 st ed., 1982, and 2nd ed., 1990.

4) Mark, E. J.: Lung Biopsy Interpretation. Williams & Wilkins, Baltimore, 1984.

5) Flint, A. and Colby, T. V.: Surgical Pathology of Diffuse Infiltrative Lung Disease. Grune & Stratton, Inc., Orlando, 1987.

6) Thurlbeck, W. M. (ed.): Pathology of the Lung, Thieme Medical Publishers, Inc., New York, 1988.

7) Yousem, S. A. et al.: Lung biopsy in rheumatoid arthritis. Am. Rev. Respir. Dis., 131: 770-777, 1985.

8) Tazelaar, H. D. et al.: Interstitial lung disease in polymyositis and dermatomyositis. Clinical features and prognosis as correlated with histologic findings. Am. Rev. Respir. Dis., 141: 727-733, 1990.

9) Epler, G. R. et al.: Bronchiolitis obliterans organizing pneumonia. N. Eng. J. Med., 312: 152-158, 1985.

10) Katzenstein, A. -L. A. et al.: Acute interstitial pneumonia. A clinicopathologic, ultrastructural, and cell kinetic study. Am. J. Surg. Pathol., 10: 256-267, 1986.

11) Kitaichi, M.: Alveolar septal inflammation: a comparative pathological study of IPF and BOOP. In: Interstitial Pneumonia of Unknown Etiology. Ed. by Harasawa, M. et al., University of Tokyo Press, Tokyo, 1989, pp. 189-199.

12) Katzenstein, A-L. A. et al.: Diffuse alveolar damage-the role of oxygen, shock, and related factors. Am. J. Pathol., 85: 210-228, 1976.

13) Carrington, C. B. et al.: Natural history and

treated course of usual and desquamative interstitial pneumonia. N. Eng. J. Med., 298 : 801-809, 1978.

14) Liebow, A. A. et al. : Desquamative interstitial pneumonia. Am. J. Med., 39 : 369-404, 1965.

15) Colby, T. V. and Carrington, C. B. : Lymphoreticular tumors and infiltrates of the lung. Pathol. Annu., 18 (1) : 27-70, 1983.

16) Imai, H. and Kitaichi, M. : A case of bronchiolitis obliterans organizing pneumonia (BOOP) showing spontaneous regression after an open lung biopsy. Nippon Kyobu Shikkan Gakkai Zassi (Jpn. J. Thorac. Dis.), 27 : 829-836, 1989 (in Japanese).

17) Yousem, S. A. et al. : Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin. Proc., 64 : 1373-1380, 1989.

18) Liebow, A. A. : New concepts and entities in pulmonary disease. In : The Lung. Ed. by Liebow, A. A., Williams and Wilkins, Baltimore, 1967, pp. 332-365.

19) Liebow, A. A. and Carrington, C. B. : The interstitial pneumonias. In : Frontiers of Pulmonary Radiology. Ed. by Simon, M. et al., Grune & Stratton, Orlando, 1968, pp. 102-141.

20) Liebow, A. A. : Definition and classification of interstitial pneumonias in human pathology. Prog. Respir. Res., 8 : 1-33, 1975.

21) Davison, A. G. et al. : Interstitial lung disease and asthma in hard-metal workers : bronchoalveolar lavage, ultrastructural, and analytical findings and results of bronchial provocation tests. Thorax, 38 : 119-128, 1983.

22) King, T. E. Jr. : Idiopathic pulmonary fibrosis. In : Interstitial Lung Disease. Ed. by Schwartz M. I. and King, T. E. Jr., B. C. Decker, Inc., Toronto, 1988, pp. 139-169.

23) Hay, J. G. and Turner-Warwick, M. : Cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) : review of certain features leading to new areas of investigation. In : Recent Advances in Respiratory Medicine. Ed. by Flenley, D. C. and Petty, T. L., Churchill Livingstone, Edinburgh, 1986, pp. 131-151.

24) Turner - Warwick, M. : Cryptogenic fibrosing alveolitis. In : Clinical Atlas. Respiratory Diseases. Ed. by Turner-Warwick, M. et al., J. B. Lippincott Co., Philadelphia, 1989, 21. 1-21. 12.

25) Crystal, R. G. et al. : Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic and biochemical aspects. Ann. Intern. Med., 85 : 769-788, 1976.

26) Crystal, R. G. : Idiopathic pulmonary fibrosis (IPF). In : Cecil Textbook of Medicine. 18th ed. . Ed. by Wyngaarden, B. and Smith, L. H., W. B. Saunders Co., Philadelphia, 1988, pp. 428-429.

27) Weissler, J. C. : Southwestern Internal Medicine Conference : Indiopathic pulmonary fibrosis : cellular and molecular pathogenesis. Am. J. Med. Sci., 297 : 91-104, 1989.

28) Izumi, T. : Fibrosing intestitial pneumonia and idiopathic pulmonary fibrosis. Nippon Kyobu Shikkan Gakkai Zassi (Jpn. J. Thorac. Dis.), 27 : 1268-1273, 1989 (in Japanese).